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APPLICATION NUMBER	FILING DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO.
09/164,588	10/01/98	NUELLE	R 012712-572

EXAMINER	
GAMBEL, P	
ART UNIT	**PAPER NUMBER**
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DATE MAILED: 06/19/01

This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

OFFICE ACTION SUMMARY

☑ Responsive to communication(s) filed on 4/4/01

☑ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 D.C. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire 3 month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☑ Claim(s) 54-63 is/are pending in the application.
Of the above, claim(s) _____ is/are withdrawn from consideration.
☐ Claim(s) _____ is/are allowed.
☑ Claim(s) 54-63 is/are rejected.
☐ Claim(s) _____ is/are objected to.
☐ Claim(s) _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.
☐ The drawing(s) filed on _____ is/are objected to by the Examiner.
☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.
☐ The specification is objected to by the Examiner.
☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.
☐ received in Application No. (Series Code/Serial Number) _____.
☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☑ Notice of Reference Cited, PTO-892
☑ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____
☐ Interview Summary, PTO-413
☐ Notice of Draftperson's Patent Drawing Review, PTO-948
☐ Notice of Informal Patent Application, PTO-152

--SEE OFFICE ACTION ON THE FOLLOWING PAGES--

★ U.S. GPO: 1996-404-496/40517

DETAILED ACTION

1. Applicant's amendment, filed 4/4/01 (Paper No. 11), is acknowledged.

Claims 54-63, as they read on "autoantigen expressing cells" are being acted upon as the elected invention.

Claims 1-53 have been canceled previously.

2. The text of those sections of Title 35 USC not included in this Action can be found in a prior Action.
This Office Action will be in response to applicant's arguments, filed 4/4/01 (Paper No. 11).
The rejections of record can be found in the previous Office Action (Paper No. 13).

3. Claims 54-63 stand rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention

Applicant's arguments, filed 4/4/01 (Paper No. 11), have been fully considered but are not found convincing essentially for the reasons of record.

Applicant asserts that the rejection in the instant application is inconsistent with the rejection set forth in copending USSN 09/223,634, where methods of treating autoimmune disorders have been determined allowable.

Applicant acknowledges that the objective evidence supporting the enablement of the claimed methods in the instant application have not been made of record herein.

Applicant cites Howard et al. (J. Clin. Invest. 103: 281-290, 1999); preliminary studies in a Reply information from a grant including a brief overview of phase I clinical trials; Liu et al. (J. Immunol. 163: 4048-4057, 1999); Stuberg et al. (J. Exp. Med 183: 693-698, 1996); Flanders et al. (Autoimmunity 29: 235-246, 1999) ;

however these references do not appear with applicant's amendment, filed 4/4/01 (Paper No. 11).

It is also noted that the instant methods differ from the claimed methods from copending applications. The claims recite a method which encompass the use of an "autoantigen expressing cell".

As pointed out previously, in reviewing antigen-specific immunotherapy, Tisch et al. (PNAS 91: 437-438, 1994) disclose that it is apparent that peptide- or antigen-specific T immunotherapy, when applied to a highly defined model of autoimmunity, can be effective. However it is unclear whether this approach is feasible in the prevention or treatment of spontaneous autoimmune disease such as multiple sclerosis, diabetes or arthritis, in which the target autoantigens are not known and a number of autoantigens appear to be involved in the disease process).

Furthermore, it is unclear whether such immunotherapy can be used to treat an ongoing autoimmune response (which is the usual case) or whether it is effective only in terms of prevention. Generally, such diseases are diagnosed only after significant tissue damage has occurred. Human autoimmune diseases comprise multiple epitopes or multiple immune responses that makes therapeutic intervention a major hurdle even for known autoimmune conditions.

Similarly, Schwartz discloses that (see pages 1052-1053 in Fundamental Immunology, Third Edition, Paul, ed. Raven Press, 1993) the task of finding disease-related autoantigens is a formidable challenge, that autoantigens are often not autospecific; and that neither the autoantibodies associated with an autoimmune disease, nor the autoantigen to which they bind necessarily incite the lesions of the disorder.

Therefore, given the lack of knowledge or predictability about the identification and the role of a particular "autoantigen" in human autoimmunity; it is not clear that the skilled artisan could predict the ability of the CD40L-specific antibodies in combination with an "autoantigen expressing cell" to inhibit autoimmune diseases, commensurate in scope with the claimed methods.

There is insufficient and guidance and direction as to the nature, characterization and role of particular autoantigens in human autoimmunity as to provide predictability of providing autoantigen expressing cells to inhibit autoantigen-specific immune responses in the treatment of autoimmunity.

In vitro and animal model studies have not correlated well with in vivo clinical trial results in patients. Since the therapeutic indices of immunosuppressive drugs such as costimulatory-based biopharmaceutical drugs can be species- and model-dependent, it is not clear that reliance on the experimental observations of inhibiting certain in vitro or in vivo immune response would be predictive of treating the breadth of autoimmune diseases encompassed by the claimed methods which rely upon the administration of an autoantigen expressing cell. There is insufficient objective evidence that accurately reflects the relative efficacy of the claimed therapeutic strategies to inhibit autoimmune diseases, commensurate in scope with the therapeutic methods encompassed by the claimed methods.

In view of the lack of predictability of the art to which the invention pertains the lack of established clinical protocols for effective antigen-specific-based therapies on inhibiting human autoimmunity; undue experimentation would be required to practice the claimed methods with a reasonable expectation of success, absent a specific and detailed description in applicant's specification of how to effectively practice the claimed methods and absent a sufficient number of working examples providing evidence which is reasonably predictive that the claimed methods are effective for inhibiting human autoimmunity with CD40L-specific antibodies and autoantigen expressing cells.

Applicant's arguments are not found persuasive.

8. Claims 54-63 stand rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a written description rejection.

The specification broadly describes and the claims recite as part of the invention the following:

"An autoantigen expressing cell(s)".

The instant methods which rely upon "autoantigen expressing cells" rely upon possession or knowledge of the "autoantigen" in order to express in an antigen presenting cell.

Applicant's arguments, filed 4/4/01 (Paper No. 11), have been fully considered but are not found convincing essentially for the reasons of record.

Applicant argues that possession of the invention does not required knowledged or isolation of specific autoantigens rather what is required is a knowledge of the types of cells that elicit autoimmunity.

For example, applicant asserts that the ordinary artisan would co-administer islet cells with a gp39 antagonist to practice the claimed invention.

In contrast to applicant's assertions, it appears that the claims are drawn to the co-administration of antigen-presenting cells expressing the appropriate autoantigen.

It appears that the claimed methods do rely upon some knowledge and possession of a particular autoantigen of interest, including possession of the particular autoantigen which is involved in the down regulation of an autoimmune response

As pointed out previously, such autoantigens do not meet the written description provision of 35 USC 112, first paragraph. Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the 'written description' inquiry, whatever is now claimed." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116.).

The skilled artisan cannot envision all the contemplated "autoantigens" encompassed by the by the detailed chemical structure of the claimed autoantigens and therefore conception cannot be not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it. The nucleic acid itself (or in this case the autoantigen) is required. See Fiers v. Revel, 25 USPQ2d 1601, 1606 (CAFC 1993) and Amgen Inc. V. Chugai Pharmaceutical Co. Ltd., 18 USPQ2d 1016. One cannot describe what one has not conceived. See Fiddes v. Baird, 30 USPQ2d 1481, 1483. In Fiddes v. Baird, claims directed to mammalian FGF's were found unpatentable due to lack of written description for the broad class.

Similarly, applicants have not disclosed sufficient information encompassing "autoantigens" and therefore clearly lacks written description for the broad class of "autoantigen expressing antigen presenting cells".

As pointed out above and in reviewing antigen-specific immunotherapy; Tisch et al. (PNAS 91: 437-438, 1994) disclose that it is apparent that peptide- or antigen-specific T immunotherapy, when applied to a highly defined model of autoimmunity, can be effective. However, it is unclear whether this approach is feasible in the prevention or treatment of spontaneous autoimmune disease such as multiple sclerosis, diabetes or arthritis, in which the target autoantigens are not known and a number of autoantigens appear to be involved in the disease process.

Therefore, it does not appear that the limited disclosure of known antigens in experimental systems in the specification as filed provides written description of the "autoantigens", particularly those involved human autoimmunity, where the autoantigens are either unknown or encompass a myriad of autoantigens, which can change during the course of the disease.

While the specification as filed discloses certain known antigens; the specification does not provide sufficient disclosure of "autoantigens", which would be presented by antigen presenting cells that meets the written description provision of 35 USC 112, first paragraph.

Applicant is reminded that Vas-Cath makes clear that the written description provision of 35 USC 112 is severable from its enablement provision. (See page 1115.).

Applicant is directed to the Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

9. Claim 57 stands rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 57 is indefinite in the recitation of "professional" antigen presenting cell. While it is acknowledged that page 9, paragraph 3 of the instant specification discloses that "professional" antigen presenting cells may be "monocytes, dendritic cells or Langerhans's cells; the metes and bounds of such "professional" APC's are unclear and ambiguous. It is unclear what differs a professional APC from an APC, provided that a cell presents antigen.

Applicant is invited to recite the particular cell types, disclosed in the specification as filed.

Applicant should specifically point out the support for any amendments made to the disclosure. See MPEP 714.02 and 2163.06

Given the absence of additional rebuttal to the outstanding rejections of record in applicant's amendment, filed 4/4/01 (Paper No. 11); the rejections are maintained for the reasons of record

10. No claim allowed.

11. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

12. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Phillip Gambel whose telephone number is (703) 308-3997. The examiner can normally be reached Monday through Thursday from 7:30 am to 6:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (703) 308-3973. Any inquiry of a general nature or relating to the status of this application should be directed to the Technology Center 1600 receptionist whose telephone number is (703) 308-0196.

Papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November

PHILLIP GAMBEL

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June 18, 2001